REMARKS

Claims 1-16 and 44-46 are pending in the application and are the subject of the present office action.

In the above amendment, claims 7 and 9 have been amended. Claim 46 has been canceled without prejudice. The amended claims are fully supported by the specification (discussed below), and accordingly, no new matter has been introduced thereby.

A "clean" version of the now pending claims 1-16, 44, and 45 is shown above.

Attached hereto is a marked-up version of the changes made to the claims and specification by the amendment. The attachment is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE".

Each of the objections and rejections set forth in the office action is addressed below.

A. Objections to Specification

The Examiner has noted various terms in the specification which should be capitalized and identified as trademarks. The specification has been amended, as shown above, to properly refer to these trademarks.

The Examiner has also noted a hyperlink citation on page 9 of the specification. Pursuant to the present requirements of the MPEP, this hyperlink citation has been deleted from the specification in the amendment above. Applicants do wish to make clear for the record that it is Applicants' position that deletion of the hyperlink does not render the specification (or the definition in which this hyperlink appears in the specification) insufficient in any way for purposes of complying with the requirements of Section 112. The hyperlink was included only to refer to yet an additional location or reference for those skilled in the art for purposes of identifying and obtaining information or methods on conducting alignments. Applicants further wish to point out that at the time the instant application was filed, the MPEP did not prohibit the use of hyperlink citation(s) in patent specifications; this MPEP rule was instead promulgated after the filing of the instant application. Accordingly, it is believed that such a hyperlink citation at the time

of filing does not adversely effect the disclosure of the present application.

B. Section 101 Rejections

The Examiner has rejected claims 1-16 and 44-46 under Section 101 on grounds that the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility. Applicants respectfully traverse this rejection.

In Example 8 of the specification, Applicants have demonstrated experimentally that the UCP4 polypeptide is a member of the family of uncoupling proteins. Applicants have shown in Example 8 that UCP4 expression in 293 cells significantly affected mitochondrial membrane potential. Those skilled in the art will readily appreciate that the modulation of mitochondrial membrane potential may be used to increase body metabolic rate (see, e.g., specification at page 37, lines 11-30). Indeed, these effects were further demonstrated *in vivo* in experiments described in Example 11. Those skilled in the art will readily appreciate the "real world" context for applying this technology in a variety of uses, for instance, in treatment or diagnosis of metabolic disorders (see, e.g., specification at pages 37-39.

Applicants further wish to point out that UCP4 expression was found exclusively in brain and spinal cord tissues (see Example 2). Accordingly, it is believed that the UCP4 molecule may also be used as a specific probe to detect human brain and spinal cord tissues.

Withdrawal of the Section 101 rejections is respectfully requested.

C. Section 112 Rejections

Claims 7, 9 and 44-46 were rejected under Section 112, first paragraph, as containing subject matter not sufficiently described in a way to show possession of the claimed invention.

Claims 7 and 9 have been amended to recite the biological activity of the polypeptide. The recited activity reflects that found by Applicants, as described in the specification. The amendment is not considered to be a narrowing amendment by Applicants, as the language incorporated into claims 7 and 9 was already provided in the definition

of "biological activity" on page 14 of the specification. For these reasons, it is believed by Applicants that the amendment does not narrow the full scope of equivalents of the claimed invention. Claim 46 has been canceled without prejudice.

It is believed that the amendments to claims 7 and 9 overcome the Examiner's rejection.

Claim 9 was rejected under Section 112, second paragraph, as being indefinite. Applicants respectfully request withdrawal of this rejection in view of the definition provided on page 9, lines 26-30 - page 10, lines 1-2. It is submitted that the term is readily understood by those skilled in the art in view of the express definition provided in the specification.

D. Section 102 Rejection

Claim 4 was rejected under Section 102(b) as being anticipated by Hillier et al. Applicants respectfully traverse the rejection.

The EST sequence of Hillier et al. is a partial polynucleotide sequence. The sequence structure alone of that EST does not teach or provide any guidance about a reading frame or that it encodes any polypeptide or fragment thereof, much less that it encodes an uncoupling polypeptide, as claimed. The Hillier et al. sequence therefore is not an enabling reference, and does not anticipate the claimed invention.

Withdrawal of the Section 102(b) rejection is respectfully requested.

Respectfully submitted,

GENENTECH, INC.

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By: Diane L Marschang

Diane L. Marschang
Attorney for the Applicants
Reg. No. 35,600

1 DNA WAY
So. San Francisco, CA 94080-4990
Phone: (650) 225-5416
Fax: (650) 952-9881

MARKED UP VERSION TO SHOW CHANGES MADE

IN THE SPECIFICATION:

In the paragraph on page 9, lines 3-25, the text has been amended as follows:

-- "Percent (%) amino acid sequence identity" with respect to the UCP4 sequences identified herein is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the UCP4 sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. % identity can be determined by WU-BLAST-2, obtained from [Altschul et al., Methods in Enzymology, 266: 460-480 (1996)[; http://blast.wustl/edu/blast/README.html]]. WU-BLAST-2 uses several search parameters, most of which are set to the default values. The adjustable parameters are set with the following values: overlap span =1, overlap fraction = 0.125, word threshold (T) = 11. The HSP S and HSP S2 parameters are dynamic values and are established by the program itself depending upon the composition of the particular sequence and composition of the particular database against which the sequence of interest is being searched; however, the values may be adjusted to increase sensitivity. A % amino acid sequence identity value is determined by the number of matching identical residues divided by the total number of residues of the "longer" sequence in the aligned region. The "longer" sequence is the one having the most actual residues in the aligned region (gaps introduced by WU-Blast-2 to maximize the alignment score are ignored). --

In the paragraph on page 31, lines 1-15, the text has been amended as follows:

-- It may be desired to purify UCP4 from recombinant cell proteins or polypeptides. The following procedures are exemplary of suitable purification procedures: by fractionation on an ion-exchange column; ethanol precipitation; reverse phase HPLC; chromatography on silica or on a cation-exchange resin such as DEAE; chromatofocusing; SDS-PAGE;

ammonium sulfate precipitation; gel filtration using, for example, [Sephadex] SEPHADEX™ G-75; protein A [Sepharose] SEPHAROSE™ columns to remove contaminants such as IgG; and metal chelating columns to bind epitope-tagged forms of the UCP4. Various methods of protein purification may be employed and such methods are known in the art and described for example in Deutscher, Methods in Enzymology, 182 (1990); Scopes, Protein Purification: Principles and Practice, Springer-Verlag, New York (1982). The purification step(s) selected will depend, for example, on the nature of the production process used and the particular UCP4 produced. --

In the paragraph on page 48, lines 3-13, the text has been amended as follows:

-- EST databases, which included public EST databases (e.g., [GenBank] GENBANK™), and a proprietary EST database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA), were searched for sequences having homologies to human UCP3. The search was performed using the computer program BLAST or BLAST2 [Altschul et al., Methods in Enzymology, 266:460-480 (1996)] as a comparison of the UCP3 protein sequences to a 6 frame translation of the EST sequences. Those comparisons resulting in a BLAST score of 70 (or in some cases, 90) or greater that did not encode known proteins were clustered and assembled into consensus DNA sequences with the program AssemblyLIGN and [MacVector] MACVECTOR™ (Oxford Molecular Group, Inc.). --

In the paragraph on page 64, lines 28-31 - page 65, lines 1-5, the text has been amended as follows:

-- Quantitative reverse-transcriptase polymerase chain reaction (RT-PCR) was used to determine the amount of UCP4 mRNA in the harvested tissues. RT-PCR was performed using mRNA samples. [Heid et al., Genome Research, 6:986-994 (1996); Gibson et al., Genome Research, 6:995-1001 (1996)]. Generally, to carry out quantitative RT-PCR, primers and probes specific to UCP4 were used ([TaqMan] TAQMAN™ Instrument, PE Biosciences, Foster City, California). Values were corrected for mRNA loading using

β-actin mRNA abundance as loading control. The following primers and probes were used: --

IN THE CLAIMS:

7. (Twice Amended) An isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least an 80% sequence identity to the sequence of amino acid residues from about 1 to about 323 of Figure 1 (SEQ ID NO: 1), wherein said encoded polypeptide [has at least one biologic activity of a native sequence UCP4 polypeptide consisting of amino acid residues 1 to 323 of Figure 1 (SEQ ID NO:1)] increases or decreases mitochondrial membrane potential or metabolic rate, or (b) the complement of the DNA of (a).

9. (Once Amended) An isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least 80% positives when compared to the sequence of amino acid residues from about 1 to about 323 of Figure 1 (SEQ ID NO: 1), wherein said encoded polypeptide increases or decreases mitochondrial membrane potential or metabolic rate, or (b) the complement of the DNA of (a).

Please cancel claim 46 without prejudice.